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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,421	12/01/2000	Ban-an Khaw	9449-016-999	4389

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 01/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,421	KHAW ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☒ Interview Summary (PTO-413) Paper No(s). *18*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/3/03 has been entered. Currently claims 1-25 and 56 are pending and currently under consideration.

OBJECTIONS MAINTAINED

Applicants have not addressed the objection regarding the IDS. Accordingly it is maintained.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 has cited the references they have not been considered.

3. The information disclosure statements filed in paper #7 on 5/30/02 and in paper #10 on 8/2/02 have been considered as to the merits before first action.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 16-25, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (US Patent# 5,851,527) in view of Torchilin (Critical review in Therapeutic Drug Carrier Systems) and in further view of Bosslet et al. (US Patent# 5,591,828).

Griffiths teach methods for detecting and treating lesions in a patient. The method entails an immunoassay method that involves the reaction of a sample from a patient with a multispecific molecule (bispecific antibody). The antibody is composed of one antibody specific for a compound to be detected and a second antibody specific for a compound foreign to the patient sample; the sample is subsequently reacted with a polymer probe.

The probe has a polymer backbone attached to a compound (i.e. biotin/avidin) and is recognizable by the second antibody (column 7 and 8). Griffiths discloses several different antigens of interest in column 10 line 35 through column 14 line 38. Therein teaching the limitations of claims 2-8.

Griffiths differs from the instant invention in failing to teach at least two detectable signal compounds further attached to the polymer backbone, wherein the polymer backbone comprises at least two detectable compounds and the probe consists of paramagnetic probes with a DTPA bispecific antibody. Specifically, Griffiths et al. does not disclose a polylysine polymer probe that comprises DTPA and at least 2 HRP's.

However, in order to achieve saturation of the epitopes, which are recognized by one of the specificities on the target cells, the teachings of Bosslet et al. on bispecific antibody with one embodiment against DTPA (see abstract and column 1) meets this limitation. Bosslet et al. showed that DTPA is very reactive toward the amino groups of the polymer. Torchilin also teaches an antibody attached to a polysine polymer backbone (page 286, paragraph 1) and to polymer backbones in general (page 276 - Fig 1, and page 286 – Fig 2).

Torchilin further teaches that in order to improve labeling efficiency, multiple chelator sites should be attached to a single antibody molecule (page 276, paragraph 3) and binding of various other groups to the polymer chain (page 277, paragraph 1) and the addition of 10 to 20 chelator residues per single antibody molecule (page 287, paragraph 2) and that each molecule of DTPA (chelating agent) possesses two reactive moieties. Therefore, the polymer probe would include at least 2 or as many as 18 detectable compounds, bound by DTPA.

Torchilin teaches the use of radioisotophic probes on page 294 and paramagnetic probes on page 296 and immunoassay methods comprising fluorescent probes (page 302).

It would have been obvious at the time the invention was made to a person having ordinary skill in the art to utilize the multispecific molecule as taught by Torchilin and Bosslet et al. to detect a binding complex comprising dual antibodies and labels with a polymer backbone in the assay technique taught by Griffiths. In order to develop a sensitive assay for antigen specificity for binding complex of interest, Torchilin showed that the configuration of the multispecific molecules was easily obtainable.

While, Bosslet et al. taught that these bispecific antibodies (i.e. multi-specific molecules) are useful in therapy and diagnosis of malignant tumors (column 1 lines 46-47). A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such compounds, because such antibody binding complex detection immunoassays (*in vivo and in vitro*) have been shown to be successful in the art. One of ordinary skill in the art would have been motivated to do this because Griffiths in view of Torchilin and Bosslet et al. teach the precise techniques and reveal the utility of such antibodies as diagnostic reagents (immunogens, immunoassay reagents) and treatment compounds for cancer.

II. Claims 1, 2-12, 16-25, and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen (US Patent# 5,482,698) in view of Torchilin (Critical review in Therapeutic Drug Carrier Systems) and in further view of Bosslet et al. (US Patent# 5,591,828).

Hansen teaches a method for detecting a cytotoxic agent. The method involves:

- a bispecific antibody or antibody fragment having a first binding site specific for an antigen and a second binding site specific for an epitope on an enzyme,
- the formation of an antibody-enzyme conjugate,
- then contacting the antibody enzyme conjugate with a soluble polymer substrate-agent conjugate.

The biospecific antibody is constructed in a variety of methods including disulfide cleavage and reformation of mixtures of whole IgG, $F(ab')_2$ fragments, fusions of more than one clone to form polymers that produce immunoglobulins having more than one specificity and can be genetically engineered (column 5, lines 9-16). Hansen also discloses that it may be advantageous to bind a plurality of antibody fragments to a to a single enzyme to increase binding affinity or efficiency to the antigen target (column 6, lines16-18). The conjugate can alternatively be tagged with a label such as, radiolabel, a fluorescent label to allow for its detection and quantification in body fluids like blood and urine (in vitro detection). See column 6, lines 28-39.

Hansen differs from the instant invention in failing to teach at least two detectable signals compounds further attached to the polymer backbone, wherein the polymer backbone comprises as many as 18 detectable compounds and the probe consists of paramagnetic probes with a bispecific antibody.

However, in order to achieve saturation of the epitopes, which are recognized by one of the specificities on the target cells, the teachings of Bosslet et al. on bispecific, antibody with one embodiment against DTPA (see abstract and column 1) meets this limitation. Bosslet et al. showed that DTPA is very reactive toward the amino groups of the polymer.

Torchilin also teaches an antibody attached to a polysine polymer backbone (page 286, paragraph 1) and to polymer backbones in general (page 276 - Fig 1, and page 286 – Fig 2). Torchilin further teaches that in order to improve labeling efficiency, multiple chelator sites should be attached to a single antibody molecule (page 276, paragraph 3) and binding of various other groups to the polymer chain (page 277, paragraph 1) and the addition of 10 to 20 chelator residues per single antibody molecule (page 287, paragraph 2) and that each molecule of DTPA (chelating agent) possesses two reactive moieties. Therefore, the polymer probe would include at least 2 or 18 detectable compounds, bound by DTPA. Torchilin teaches the use of radioisotophic probes on page 294 and paramagnetic probes on page 296 and immunoassay methods comprising fluorescent probes (page 302).

Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to utilize the multispecific molecule as taught by Torchilin and Bosslet et al. to detect a binding complex comprising dual antibodies and labels with a polymer backbone in the assay technique taught by Hansen in order to develop a sensitive assay for antigen specificity for binding complex of interest, Torchilin showed that the configuration of the multispecific molecules was easily obtainable.

While, Bosslet et al. taught that these bispecific antibodies (i.e. multi-specific molecules) are useful in therapy and diagnosis of malignant tumors (column 1 lines 46-47). A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such compounds, because such antibody binding complex detection immunoassays (*in vivo and in vitro*) have been shown to be successful in the art.

One of ordinary skill in the art would have been motivated to do this because Hansen in view of Torchilin and Bosslet et al. teach the precise techniques and reveal the utility of such antibodies as diagnostic reagents (immunogens, immunoassay reagents) and treatment compounds for cancer.

III. Claims 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths (US Patent# 5,851,527) or Hansen (US Patent# 5,482,698) in view of Torchilin (Critical review in Therapeutic Drug Carrier Systems) and in further view of Bosslet et al. (US Patent# 5,591,828).

Please see Griffiths or Hansen in view of Torchilin and further in view of Bosslet et al. as set forth above.

Griffiths or Hansen in view of Torchilin and further in view of Bosslet et al. differ from the instant invention in not particularly citing the molar concentration of the antigen present in the sample. However all the references give concentrations with respect to the reagents utilized. For example see Griffiths column 17 to column 23 and Hansen column 17 to column 19.

One of ordinary skill in the art would utilize various concentrations of the antibody for the resulting data sets to evaluated the antigen of interest in assay procedures.

The variation of reagent concentration is routine optimization that is almost always determined and used in immunoassay studies. Unless the result obtained in the instant application is a significant and unexpected difference over the prior art, it would have been prima facie obvious for one of ordinary skill in the art to modify reagent concentration in the given parameters to determine the unknown as a means of optimizing the assays provided by the art.

Absent results to the contrary or unexpected results the modification is viewed as an obvious modification that does not render the claims patentably distinct from Griffiths or Hansen in view of Torchilin and further in view of Bosslet et al.

Response to Arguments

5. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., non-endogenous antigen) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant contends that the instant method is performed in specific steps, this argument has been carefully considered but not found persuasive because merely revising the order of the steps of a multi-step process does not impart patentability when no unexpected result is obtained. *Ex parte Rubin* (POBA 1959) 128 USPQ 440; *Cohn v.Comr. Pats.* (DCDC 1966) 251 FSupp 437, 148 USPQ 486. Similarly, a two step combination and two obvious process steps is unpatentable when each lends properties to the final product known to be produced when the step is practiced alone, in the absence of evidence of coaction between the steps which produce an unobvious result. *In re Fortess* (CCPA 1966) 369 F2d 1009, 152 USPQ 13.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., covalent linkage of the antibody and polymer in Griffiths and Hansen, direct conjugation in Torchilin, and whole antibody vs. antibody fragments in Bosslet) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Griffiths teaches an immunoassay method that involves the reaction of a sample from a patient with a multispecific molecule (bispecific antibody). The antibody is composed of one antibody specific for a compound to be detected and a second antibody specific for a compound foreign to the patient sample, the sample is subsequently reacted with a polymer probe. The probe has a polymer backbone attached to a compound (i.e. biotin/avidin) and is recognizable by the second antibody (column 7 and 8). Griffiths differs from the instant invention in failing to teach at least two detectable signal compounds further attached to the polymer backbone.

The addition of this limitation is taught as an improvement for labeling efficiency. See discussion of Torchilin. Therefore, it would have been obvious at the time the invention was made to a person having ordinary skill in the art to utilize the multispecific molecule as taught by Torchilin to detect the binding complex of Griffiths comprising dual antibodies and labels with a polymer backbone in order to develop a sensitive assay for antigen specificity for binding an antigen of interest.

While, Bosslet et al. taught that these bispecific antibodies (i.e. multi-specific molecules) are useful in therapy and diagnosis of malignant tumors (column 1 lines 46-47). A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such compounds, because such antibody binding complex detection immunoassays (*in vivo and in vitro*) have been shown to be successful in the art. One of ordinary skill in the art would have been motivated to do this because Griffiths in view of Torchilin and Bosslet et al. teach the precise techniques and reveal the utility of such antibodies as diagnostic reagents (immunogens, immunoassay reagents) and treatment compounds for cancer.

6. For reasons aforementioned, no claims are allowed.

Remarks

7. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Khaw et al. (WO 90/15993) teach a monoclonal antibody with utility in forming an immune complex with human ventricular myosin LC1, and having no binding affinity for human fast skeletal myosin LC1.

B. Goldenberg (U.S Patent #5,332,567) discloses methods of detecting and treating of infections with immunoconjugates.

C. Chang et al. (WO 94/12196) evaluates conjugates and constructs including anti-CD28 or anti-CD# binding molecules and polymers, or other backbones.

D. Goldenberg (U.S. Patent #5,698,178) disclosed polyspecific immunoconjugates and antibody composites for targeting the multidrug resistant phenotype.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Central Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to send an unofficial fax, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
Patent Examiner
Art Unitt: 1641
CM1 7B17
12/13/03

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12/24/03